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Blood-based biomarkers of cancer-related cognitive impairment in non-central nervous system cancer: protocol for a scoping review

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ABSTRACT

Introduction Cancer-related cognitive impairment (CRCI) can have detrimental effects on quality of life, even among patients with non-central nervous system (CNS) cancers. Several studies have been conducted to explore different markers associated with CRCI to understand its pathobiology. It is proposed that the underlying mechanisms of CRCI are related to a cascade of physiological adaptive events in response to cancer and/or treatment. Hence, peripheral blood would be a logical source to observe and identify these physiological events. This paper outlines the protocol for a scoping review being conducted to summarise the extant literature regarding blood-based biomarkers of CRCI among patients with non-CNS cancer.

Methods/analysis Methods will be informed by the updated guidelines of Arksey and O'Malley. The systematic search for literature will include electronic databases, handsearching of key journals and reference lists, forward citation tracking and consultation with content experts. Study selection will be confirmed by duplicate review and calculation of inter-rater reliability. Data to be charted will include study design, sample size, cancer and treatment characteristics, demographic characteristics, cognitive variable/s and biomarkers assessed, associations between cognitive functioning and biomarkers (including statistics used), and rigour in biomarker sample collection and processing. Results will be presented through: (1) a descriptive numerical summary of studies, including a flow diagram based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement, (2) a list of blood-based biomarkers associated with CRCI and (3) a narrative overview developed through collaboration among the research team and consultation with content experts.

Dissemination The findings of this review will highlight current directions and gaps in the current body of evidence that may lead to improved rigour in future CRCI investigations. The dissemination of this work will be facilitated through the involvement of clinicians and researchers on the research team, an external consultation process and the presentation of the results through scholarly publication and presentation.

Strengths and limitations of this study

- ► This review will apply scoping review methodology to map the literature regarding blood-based biomarkers of cancer-related cognitive impairment.
- ► Interpretation of the data will involve the collaboration of clinicians, researchers and content experts.
- ► The review will be limited to research conducted in adults with non-central nervous system cancers and published in English.

INTRODUCTION

Improved survival after cancer treatment has led to greater impetus to minimise the long-term adverse effects of the disease and its treatment. Cancer-related cognitive impairment (CRCI) is now widely regarded as a prevalent and clinically significant issue among adult patients with non-central nervous system (CNS) tumours, particularly after systemic treatment with chemotherapy.[1 2] CRCI is typically characterised by problems in memory, attention, processing speed and executive functioning.[3 4] The potential consequences of CRCI on survivors' quality of life are significant, including challenges with emotional well-being, return to work and ability to engage effectively in self-care[5 6] in the months to years after treatment.

Numerous reviews of clinical studies of patients with non-CNS cancer indicate wide variation in the severity, trajectory and duration of CRCI that can be expected after cancer treatment.[7–13] Estimates of prevalence have also varied widely, ranging from 17% to 75% of patients depending on how CRCI is measured.[12 14–16] CRCI has demonstrated associations with a range of factors, such as treatment severity, overall functional status and affective symptoms, but study findings are largely mixed.[12 16 17] Ultimately, the identification of patients most likely to experience persistent negative cognitive outcomes remains unclear and effective interventions for routine use have yet to be established.[18–20]

To address these gaps, a greater understanding of the biological mechanisms underlying CRCI is needed.

Several candidate mechanisms of CRCI have been proposed, including inflammation and cytokine dysregulation, chemotherapy-induced epigenetic changes, blood–brain barrier disruption, hormone deficiencies, oxidative DNA damage and shortened telomere length, and genetic susceptibility.[21–26] However, the heterogeneity and design limitations within the emerging body of evidence have led to recommendations for harmonising study methodologies and moving towards multisite, longitudinal research.[3 27] Such approaches would support the demonstration of robust relationships between measurable biological processes and cognitive outcomes.

In this context, peripheral blood is appealing as a biomarker data source in CRCI research. Biomarkers or biological markers have been broadly defined as 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to therapeutic intervention' (Biomarkers Definition Working Group, p89).[28] Peripheral blood offers a rich source of circulating proteins, metabolites, cells and genomic markers that may reflect processes underlying CRCI. For example, cytokines produced in the periphery reach the brain through several pathways, including directly through the blood–brain barrier, to stimulate microglia and other immune cells to secrete proinflammatory cytokines in the brain, which at elevated levels can produce negative effects to learning, memory and neuronal plasticity.[29] Bringing together the current evidence related to CRCI biomarkers in peripheral blood will suggest priority biomarkers for future investigation in this area, thereby facilitating consistency in research approaches and advancement towards large prospective studies. In addition, aligned with the movement towards personalised medicine, the determination of sensitive and specific blood-based biomarkers could potentially prove useful in stratifying risk for poor cognitive outcomes and guiding treatment decision-making in clinical practice.

The purpose of this paper is to report our protocol for a scoping review that will summarise the extant literature regarding blood-based biomarkers of cognitive impairment among patients with non-CNS cancer. A scoping review methodology was chosen as it facilitates a characterisation of the range and extent of existing evidence available on a given topic, particularly when a body of literature is emerging and expected to be heterogeneous in nature.[30 31] Such evidence is often not amendable to systematic review methods that employ stringent selection criteria and quality appraisal processes aimed to answer narrowly focused questions, primarily of intervention effectiveness.[30] While detailed evidence reviews related to select hypothesised biological mechanisms of CRCI have been previously published,[21–23 32] we describe in this paper our approach to map the evidence on the potential array of blood-based biomarkers for CRCI more broadly. Such work will inform priority research areas and opportunities for moving towards the identification of blood-based biomarkers that are clinically significant and feasible to collect. The study will follow the methodology of Arksey and O'Malley[31] and refined by Levac *et al*,[33] which outlines a six-stage process for conducting scoping reviews.

METHODS

Stage 1: identifying the research question

The scoping review is guided by the following research question:

- What blood-based biomarkers have been associated with CRCI in patients with non-CNS cancer?

For the purposes of this review, blood-based biomarkers are operationalised as molecular indicators detected in blood, blood products, plasma or serum. We define CRCI as difficulties in thinking processes, including but not limited to memory, attention, concentration, processing speed and executive functioning among patients with a cancer diagnosis.[3 34 35]

Stage 2: identifying relevant studies

The search for relevant studies will incorporate electronic databases, handsearching of key journals, review of reference lists, forward citation tracking and consultation with experts in CRCI and symptom science. Search strategies were developed by an academic health science librarian (APA) with input from project leads. A comprehensive search of electronic databases involved MEDLINE (Ovid MEDLINE 1946 to January Week 4 2017, Ovid MEDLINE In-Process and Other Non-Indexed Citations 6 February 2017), EMBASE (Embase Classic+Embase 1947 to 26 February 2017), PsycINFO (PsycINFO 1974 to January Week 5 2017), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1 January 2006 to 7 February 2017), Cochrane Central Register of Controlled Trials (CENTRAL) and grey literature. The search strategies were translated using each database platform's command language, controlled vocabulary and appropriate search fields. Medical subject headings (MeSH), EMTREE terms, American Psychological Association thesaurus terms, CINAHL headings and textwords were used to search the concepts of synonyms of 'blood', 'biological markers', 'neurocognitive impairment' and 'cancer'. Language limits were applied to capture articles in English in all databases, where applicable. Publication date limits were also applied to capture articles published from 2006 to present. Final searches were completed in February 2017. The full MEDLINE search strategy is provided in online supplementary appendix A.

The database search will be supplemented by: (1) hand searches of the table of contents for the past 10 years of key journals known to publish studies related to CRCI (see box); (2) review of reference lists of included studies ('snowballing') and (3) forward citation tracking of included studies in Scopus and Web of Science. Consultation with content experts, including authors of included

Box List of journals for hand search

- *Annals of Oncology*
- *Blood*
- *Brain, Behaviour, and Immunity*
- *Journal of Clinical Oncology*
- *Journal of Pain and Symptom Management*
- *Journal of Psychosomatic Research*
- *Psycho-Oncology*
- *Psychosomatic Medicine*
- *Supportive Care in Cancer.*

studies and individuals identified through our collective research networks, will also be conducted to determine if known relevant articles have been missed.

All records retrieved will be downloaded into a bibliographic software (EndNote) where duplicates will be removed and recorded. Finally, citations will be uploaded to Covidence, an internet-based software programme designed to facilitate review data management and collaboration between reviewers during the study selection process.

Stage 3: study selection

Studies selected for the scoping review will be included if they: (1) are clinical studies of patients with a cancer diagnosis; (2) enrolled adults (≥18 years of age); (3) include a measurement of blood-based biomarkers; (4) include a subjective or objective assessment of cognitive functioning; (5) report on the association between the biomarker and cognitive functioning and (6) are written in English. Studies will be excluded that focus on cancers of the CNS or paediatric cancer, due to likely differences in pathology of cognitive impairment in these populations. Case reports, editorials, letters, literature reviews, meeting abstracts and dissertations will be excluded.

Study selection will occur through two phases using the Covidence platform. In phase I, titles and abstracts of citations will be screened for relevance in duplicate, by two independent reviewers, based on the research question and inclusion/exclusion criteria. Citations determined as relevant will be retrieved in full-text and proceed to phase II screening. In phase II, the inclusion and exclusion criteria will be applied to each of the full-text articles by two independent reviewers. Included studies will form the basis of the scoping review; otherwise, reasons for study exclusion after full-text review will be documented. In both phases of study selection, inter-rater reliability between reviewers on determinations of study inclusion will be assessed by calculating a Cohen's κ statistic,[36] and strong agreement ($\kappa \leq 0.80$)[37] will be ensured prior to proceeding. Any disagreements between the two reviewers will be resolved by a third reviewer.

Given the exploratory and iterative nature of scoping studies, reviewer meetings throughout the course of the study selection process will allow for the discussion, clarification and refinement of inclusion/criteria as needed.[31 33]

Stage 4: charting the data

'Charting' the data involves the standardised collection of key items of information from the included studies, which will form the basis of the analysis.[31] A data charting form developed by the research team will be used to ensure that the most appropriate data is collected from each study to answer the research question. The data to be extracted from each study will include: publication year, study location, study aim, study design, sample size, cancer diagnoses, severity of disease (eg, metastatic, non-metastatic), cancer treatment received, demographic characteristics (eg, age, sex), cognitive measure(s) (eg, name of questionnaires or neuropsychological tests), cognitive variable measured (eg, attention, verbal memory, executive function), biomarker assessed, biomarker sample source (eg, serum, plasma), association between cognitive functioning and biomarkers, and statistical approach used in determining association. Scoping reviews typically do not involve a formalised quality assessment of included studies,[31 33] however, including a consideration of methodological characteristics of existing studies can facilitate the identification of gaps in the evidence base.[38] As such, data will also be collected from each study regarding documented rigour in biomarker sample collection (eg, timing), processing and testing (eg, preparation, storage, assay protocol), and analysis (eg, replication), as available. Data charting fields may be further updated on closer consideration of the included studies.[33]

Independent data extraction by two reviewers (MA, WB) on a shared 10 studies will be used to assess clarity of the data charting form and consistency across reviewers. Discrepancies will be discussed in collaboration with the principal investigator (SJM) and revisions made to the data charting form as required. After consistency between reviewers is established, each additional included study will have data extracted by a single reviewer (MA or WB). Data extraction for each study will be further reviewed by one of the study investigators to ensure accuracy.

Stage 5: collating, summarising and reporting the results

This stage will be composed of three steps, as recommended by Levac *et al*[33]: (1) analysing the data; (2) reporting results and (3) applying meaning to the results. In the first step, data analysis will involve a descriptive numerical summary analysis and a qualitative analysis. The descriptive numerical summary will include a description of included studies, such as number of studies included types of study designs, sample characteristics, cognitive assessment tools and biomarkers assessed. In addition, a flowchart based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement[39] will be added to present the flow of studies through the scoping review screening process. A qualitative summary of the results will be developed with involvement from all members

of the research team, who will work collaboratively to review the data for overarching patterns and themes. In the second step, a list of the blood-based biomarkers that have shown associations with cognitive functioning will be reported, with details of the relevant evidence about these relationships. In the third step, the broader meaning of the results will be considered through a narrative overview that will characterise dominant lines of research regarding potential blood-based biomarkers of cognitive functioning, identify opportunities and gaps in the current body of evidence, and the potential implications on clinical practice, policy and future research.

Stage 6: consultation

Consultation allows for broader stakeholder involvement in the interpretation of the available literature. While stakeholders representing extensive clinical and research expertise in oncology are engaged as part of the research team, a consultation process will be undertaken to engage feedback from external stakeholders that will inform the final presentation of results. Specifically, diverse perspectives from relevant practice, policy and research arenas will be sought through presentation of preliminary findings at various academic conferences and meetings, in order to enhance the validity and impact of this review.

ETHICS AND DISSEMINATION PLAN

Overall, the current review will characterise dominant lines of research regarding potential blood-based biomarkers of cognitive functioning, emerging topics and gaps in the current body of evidence, and implications of the design of future work in this area. The results of this review will contribute to the refinement of research efforts to identify blood-based biomarkers that are clinically significant and feasible to collect. The dissemination of this work is facilitated through an integrated knowledge translation approach, which includes the involvement of clinicians and researchers on the research team and an external consultation process. Moreover, the presentation of the results through scholarly publication and presentation will contribute to its uptake. The expected study end date for this work is February 2018. Ethical approval for this review is not required.

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